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COMPLETE SPECIFICATION

Emzymic Composition

I, IRVING INNERFIELD, a citizen of the United States of America, of 20, Knickerbocker Road, Tenafly, State of New Jersey, United States of America, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to a composition of matter in a dry form suitable for oral administration containing streptokinase and a pharmaceutical acceptable carrier.

It will be understood that the term streptokinase includes kinases (enzyme activators) which are produced by bacteria other than the streptomyces bacteria from which the streptokinase is obtained, and which are also capable of the same enzyme activation as streptokinase.

An object of the invention is the provision of a composition containing streptokinase and a pharmaceutically acceptable carrier which is of marked efficacy when administered orally, e.g., sub-lingually, including especially buccally.

Another object of the invention is to provide a composition containing streptokinase and a pharmaceutically acceptable carrier which is not only suitable for oral administration but which when entericly coated, is unaffected in the stomach.

A further object of the invention is the provision of a composition containing streptokinase and a pharmaceutically acceptable carrier which is stable with retention of its potency for extended periods of time.

A still further object of the invention is the provision of a streptokinase and pharmaceutically acceptable carrier-containing composition which may be produced readily, economically and efficiently to a desired extent.

A particular object of the invention is to provide a composition of matter, in dry condition containing streptokinase in conjunction with other substances including a pharmaceutically acceptable carrier, thus a dried animal substance such as a dried plasma, e.g. dried human plasma, and further the composition may be provided with an enteric envelope.

In the practice of the invention, a composition of matter in dry condition, is produced which contains streptokinase in conjunction with at least one other substance, (including a pharmaceutically acceptable carrier), for example a dried animal substance selected from dried placental tissue, muscle tissue, amniotic fluid and a plasma, suitably dried human plasma. Further, the composition may be in the form of a tablet or of a powder enclosed in a capsule, such as a gelatin capsule. Moreover, the tablet and the capsule may have an outer coating of an enteric substance, or the capsule may consist of an enteric substance. The animal substance may be dried in any suitable manner, and preferably by lyophilizing.

Additionally, I have found that for buccal administration, the efficacy of a streptokinase-containing composition is materially improved by the inclusion of a pharmaceutically acceptable carrier which is a salivant such as saccharin, i.e. benzo sulphimide, $C_6H_4COSO_2NH$, and "Sucaryl", i.e. sodium, potassium and calcium salts of cyclo hexyl sulphamic acid, $C_6H_{11}NHSO_3H$, present in an amount from 1/128 to 1/32 grain, suitably 1/64 grain, per dosage unit.

Furthermore, the source of the plasma may be other than human, for example, bovine, sheep, horse and pig plasma may be utilized. More particularly, the plasma may be aged plasma. The aged plasma may be prepared suitably by retaining the plasma at room temperature for a period of at least three weeks, and which period may be extended to a period of about three months, such aging being desirable since thereby loss of virility

[*Price* 3*s.* 6*d.*]

of the virus causing jaundice is effected. Additionally, the aged plasma may be dried by lyophilizing, i.e. freeze drying.

The aged plasma may be activated, e.g. by adding streptokinase to plasma and incubating for from five minutes to one-half hour at room temperature, and it is to be understood that the expression aged plasma refers not only to the aged plasma *per se* but also to the globulin fraction containing plasminogen which is separated by acidification from plasma at a pH 5.0—5.9.

It may be mentioned also that when preparing the aged plasma, it is desirable to subject it to ultra-violet irradiation.

The composition may contain a non-toxic compound as an excipient (which may be the pharmaceutically acceptable carrier or a part thereof) and utilization may be made of inorganic or of organic non-toxic compounds and more especially, of the following: starch, soluble starch, lactose, magnesium oxide, magnesium carbonate, magnesium hydroxide, aluminium hydroxide, galactose, dextrin and dextrose. Additionally, the composition may include a water soluble stabilizing and solubilizing agent, e.g. "Carbowax", which is a solid polyethylene glycol having a molecular weight e.g. of 1500 and of 4000, and which augments the stability and causes the composition to dissolve readily. The "Carbowax" may be utilized alone with the streptokinase, and also in conjunction with other substances, viz. a dried animal substance and/or a salivant, e.g. saccharin and "Sucaryl". The amount of "Carbowax" may be from 50 mgm. to 250 mgm. per dosage unit, suitably about 100 mgm. Other water soluble stabilizing and solubilizing agents that may be employed along with or in place of "Carbowax", and in like manner and in like amounts, are the following: a gum, as karaya, tragacanth, agar, gum arabic, indian gum, cherry gum and plum gum; a carbohydrate and derivatives thereof, e.g. sorbitol, sorbitol laurate, sorbose, sorbitan, mannitol, mannitol laurate, manitan, dulcitol, dextrose, soluble starch, dextrin, levulose, inositol, arabinose and beta lactose; methyl cellulose, gelatin and sodium chloride.

The envelope or coating of an enteric substance may be composed of, for example salol, shellac tolu, stearic acid, mastic, sandarac and cetyl alcohol.

Other substances that may be included are insulin and an antibiotic, e.g. penicillin, streptomycin, aureomycin, "Chloromycetin" and "Terramycin" (Registered Trade Marks).

Further, the tableting and encapsulating may be in accordance with usual pharmaceutical practice and, as above indicated, the tablets may be enveloped or coated with an enteric substance and the capsule may of itself be enteric, and if not as a gelatin capsule, then such capsule would carry an envelope of an enteric substance.

Furthermore, the composition may have a content of streptokinase from 5000 to 150,000 units of streptokinase per dosage unit, and particularly from 10000 to 100,000 units of streptokinase, and preferably from 15000 to 30000 units, and from 10 mgm. to 75 mgm. of the dried animal substance, as a dried plasma, and specifically dried human plasma; it being understood that a dosage unit is either a tablet or a capsule as produced for administration. Each 1000 units of streptokinase represents about 0.06 mgm. of streptokinase.

A dosage unit containing the enzymic substance would preferably contain about 15000 units of streptokinase and about 50 mgm. of dried human plasma. The content of the salivant would be as stated above. Additionally, the tablets and the capsules may be prepared so that a single tablet or capsule constitutes a dose, and also, in lesser units, which would necessitate more than one tablet or capsule for a desired dosage.

As an illustrative embodiment of a manner in which the invention may be practised, the following examples are presented:—

EXAMPLE I

15000 units of streptokinase are thoroughly admixed with 10 mgm. of dried human plasma and a pharmaceutically acceptable carrier and the admixture thus produced is tableted, or encapsulated.

EXAMPLE II

A composition is produced as in Example I utilizing 30000 units of streptokinase, and 50 mgm. of dried human plasma.

EXAMPLE III

15000 units of streptokinase are combined thoroughly with 75 mgm. of dried human plasma and a pharmaceutically acceptable carrier. The composition so obtained is enclosed in a gelatine capsule of suitable size, and if desired, the capsule may be entericly coated with salol.

EXAMPLE IV

30000 units of streptokniase and 50 mgm. of dried human plasma are combined as by triturating in a mortar with a pharmaceutically acceptable carrier and the composition so produced is then tableted.

EXAMPLE V

15000 units of streptokinase, 10 mgm. of dried human plasma and 275 mgm. of lactose are thoroughly admixed and the admixture thus produced is tableted.

EXAMPLE VI

30000 units of streptokinase, 50 mgm. of dried human plasma and 250 mgm. of

magnesium hydroxide are thoroughly combined. The composition thus obtained may be enclosed in a gelatine capsule of suitable size, and, if desired, the capsule enterically coated with salol.

EXAMPLE VII

15000 units of streptokinase and 100 mgm. "Carbowax" 4000 are thoroughly admixed with 75 mgm. of dried human plasma and the admixture thus produced is tableted, or encapsulated.

EXAMPLE VIII

15000 units of streptokinase, 100 mgm. "Carbowax" 4000, 100 mgm. lactose and 50 mgm. of dried human plasma, are thoroughly admixed and the admixture thus produced is tableted.

EXAMPLE IX

15000 units of streptokinase and 100 mgm. "Carbowax" 4000 are thoroughly admixed and the admixture thus produced is tableted.

EXAMPLE X

15000 units of streptokinase and 100 mgm. beta lactose are thoroughly admixed and the admixture thus produced is tableted.

EXAMPLE XI

15000 units of streptokinase, 100 mgm. "Carbowax" 4000 and 1/128 grain "Sucaryl" are thoroughly admixed with 75 mgm. of dried human plasma and the admixture thus produced is tableted.

EXAMPLE XII

15000 units of streptokinase, 100 mgm. "Carbowax" 4000 and 1/4 grain of saccharin are thoroughly admixed and the admixture thus produced is tableted.

EXAMPLE XIII

15000 units of streptokinase, 100 mgm. "Carbowax" 4000, 100 mgm. lactose and 1/4 grain of saccharin are thoroughly admixed and the admixture thus produced is tableted.

EXAMPLE XIV

15000 units of streptokinase, 100 mgm. "Carbowax" 4000 100 mgm. lactose, 1/128 grain "Sucaryl" and 50 mgm. dried human plasma are thoroughly admixed and the admixture thus produced is tableted.

EXAMPLE XV

15000 units of streptokinase, 100 mgm. beta lactose and 1/32 grain of saccharin are thoroughly admixed and the admixture thus produced is tableted.

EXAMPLE XVI

15000 units of streptokinase, 100 mgm. beta lactose and 1/64 grain of "Sucaryl" are thoroughly admixed and the admixture thus produced is tableted.

The following clinical results and case history illustrate the efficacy of the enzymic compositions according to this invention when administered orally. A particularly effective manner of administration is sub-lingual, i.e. by placing a tablet or a capsule under the tongue, and also buccally.

V. G., a 25 year old housewife who delivered a healthy baby but developed acute thrombophlebitis four days following delivery. The patient was given a capsule containing streptokinase (15000 units), a pharmaceutically acceptable carrier, and aged dried human plasma (75 mgm.) three times daily. On the third day there was no longer any sign of thrombophlebitis and the patient was permitted to get out of bed. There were no complications to the treatment.

The foregoing evidences clearly that the composition containing streptokinase, a pharmaceutically acceptable carrier, and a dried animal substance which is dried placental tissue, muscle tissue, amniotic fluid and a plasma, suitably dried human plasma, possesses marked utility, is effective and reliable when orally administered, suitably sub-lingually, and especially buccally, in the treatment for the dissolution of blood clots in arteries and in veins, as in thrombophlebitis, and for chronic neurodermatitis. It may be utilized also in the treatment of coronary thrombosis and cerebral thrombosis; and to alleviate various infections as boils, abscesses, cellulitis and diabetic carbuncles.

The administration of a substance buccally, e.g. sub-lingually, requires that the substance pass through the mucous membrane, i.e. a connective tissue, in order to be effective. The passage of the substance depends upon the relative size of the pores of the tissue and the size of the molecules of the substance. When the molecular size is relatively large, the substance is prevented from passing. The streptokinase composition, on buccal administration, causes a modification of certain substances forming a part of the oral tissue so as to increase the permeability of the same thereby permitting substances of large molecular size to pass through the mucous membrane and enter the blood stream.

A further and distinctive feature of the invention which attends the use of a salivant as or as part of the pharmaceutically acceptable carrier is that the salivant causes an increased flow of saliva, which increases the amount of plasminogen in association with the streptokinase, thereby enhancing the action of streptokinase. The efficacy of the buccal streptokinase composition is deemed to be due to the transformation of the plasminogen of the saliva to plasmin. Hence, an increase in the flow of saliva augments the amount of plasminogen and accordingly the amount of plasmin. Furthermore, the streptokinase composition may be administered

orally with attending transformation of plasminogen to plasmin, inasmuch as the various body fluids, including blood, have a plasminogen content.

WHAT I CLAIM IS:—

1. A composition of matter in dry form suitable for oral administration which contains streptokinase and a pharmaceutically acceptable carrier.

2. A composition according to Claim 1, wherein the pharmaceutically acceptable carrier is an excipient, or a water-soluble solid polyethylene glycol, or a salivant, or a mixture thereof.

3. A composition according to Claim 2, wherein the excipient is a water-soluble carbohydrate.

4. A composition according to Claim 3 wherein the carbohydrate is lactose.

5. A composition according to Claim 2, wherein the polyethylene glycol possesses a molecular weight of 4000.

6. A composition according to Claim 2, wherein the salivant is saccharin or a sodium, potassium or calcium salt of cyclohexyl sulphamic acid.

7. A composition according to Claim 1 or 2 containing as an additional ingredient, a dried animal substance selected from dried placental tissue, muscle tissue, amniotic fluid or plasma.

8. A composition according to Claim 7, wherein streptokinase is present in an amount from 5000 to 150,000 units and the dried animal substance in an amount from 10 mgm. to 75 mgm. per dosage unit.

9. A composition of matter in dry form suitable for oral administration containing streptokinase in an amount of about 15000 units and dried human plasma in an amount of from about 50 mgm. per dosage unit and, in addition, a pharmaceutically acceptable carrier.

10. A composition of matter in dry form suitable for oral administration containing streptokinase, dried plasma and an excipient.

11. A composition according to Claim 10, wherein the excipient is lactose.

12. A composition of matter in dry form suitable for oral administration containing streptokinase, a water-soluble solid polyethylene glycol and a dried animal substance selected from dried placental tissue, muscle tissue, amniotic fluid and plasma.

13. A composition according to Claim 12, wherein the polyethylene glycol possesses a molecular weight of 4000 and the plasma is human plasma.

14. A composition of matter in dry form suitable for oral administration containing streptokinase, a dried plasma and a salivant.

15. A composition of matter in dry form suitable for oral administration containing streptokinase, a dried plasma, a salivant and a water-soluble solid polyethylene glycol.

16. A composition according to Claim 15, wherein the polyethylene glycol possesses a molecular weight of 4000.

17. A composition of matter in dry form suitable for oral administration substantially as described in the examples.

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